SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY METHODS

Quality Control for Intervention Delivery

Teams of villagers (three per supplement in each village, for a total of nine per village) were recruited to prepare, portion and serve the supplements, and record attendance and consumption. Community Health Workers and bakers who had worked on previous studies with us were hired preferentially, with additional personnel as needed to make up numbers. We required at least one literate person per group of three to ensure capacity for recording child attendance and consumption. The distribution of activities within teams were decided by the teams themselves. Tasks included telephone coordination with the Bissau study coordinators for restocking ingredients, reporting any adverse events, and addressing any other issues that arose; storage of ingredients in a secured, clean room; collecting wood and making the fires for cooking Fortified Blended Food (FBF) and Control supplements; mixing/cooking, portioning and serving the supplements; recording supplement attendance and leftovers; and observing supplement consumption. In addition, on days when the Bissau research team were not present, one village team member was responsible for taking date-stamped photographs to confirm that the supplement was prepared and distributed. The teams also took it upon themselves to learn the methods of the other teams within their villages, so that, in case of a personnel absence, all tasks could be covered by another person with staggered supplement times.

A mostly experiential process was implemented to train the teams to follow methods exactly including accurate measurements and hygienic techniques, with simple written instructions and clear visuals for reinforcement. There were two regional trainings given shortly before the study launch, which were led by the Bissau research coordinators (RC, AS) with a Tufts team member present. These half-day meetings included a demonstration of ingredients, accurate measurement of ingredients and portions (volumetric, with all measuring containers provided), supplement preparation methods and hygiene, how to keep records of consumption and accounting for leftovers with provided data forms (0%, 25%, 50%, 75% or 100%), time for practicing all activities, and time for questions. Then, after baseline outcomes were complete, the Bissau research coordinators gave the local team the list of children in each randomized group, and provided continuous supervision of the supplement launch by the village teams until all methods and record keeping were error-free. This oversight was typically implemented for 2-4 days, after which time the Bissau coordinators came to the village on two random days per week to supervise supplement preparation and consumption, provide feedback as needed to maintain quality control, and restock ingredients (1 time per week or month depending on the ingredient). On other days the village teams made a date-stamped photographic record of preparation and consumption, which the coordinators reviewed weekly.

To minimize field errors, the preparation and portioning of the supplement was made as simple as possible. In the case of the new supplement (NEWSUP), the imported ingredients (high-flavanol cocoa, green tea, protein sources, essential fatty acids, fortified vegetable oil, a vitamin-mineral mix, and *moringa oleifera*) were premixed and provided in sealed bags with the correct amount for each village. The village team was trained to re-mix the bag ingredients and thoroughly mix in measured amounts of the local ingredients (peanut butter, honey, sugar) and filtered water. Preparations of the FBF and Control foods were simpler, and in these cases the ingredients were provided in bulk for daily volumetric measurements. All portions were implemented as volumetric measures, with suitable measuring devices provided.

Caregivers brought younger children to the supplement centers, while older children came alone. Handwashing with soap and water prior to consumption was implemented in all sites. Children and their parents learned which supplement center supplied their food on the first day and went directly to that location on subsequent days. Portions were given to names on the registry and attendance recorded. When the child finished eating, the record keeper recorded complete consumption or fraction of leftovers, and the remainder was taken home without specific instructions. In calculating supplement consumption, we assumed that leftovers taken home were not consumed by the study participant. Absent children received no supplement that day.

Description of Outcome Assessments
Outcomes were performed by 16 trained per diem staff who had no role in the intervention, were previously trained for nutrition outcome assessments,[1-3] and were supervised by a Tufts study coordinator (SFT) and the lead scientist for Near-Infrared Spectroscopy (NIRS) and Diffuse Correlation Spectroscopy (DCS) (MAF).

Cognition. Many of the previous studies of nutritional supplementation and cognition used composite scores across several measures of cognitive development (e.g., attention, language, motor skills), and used standardized tests of cognitive development that have not been normed to international populations or children at risk for undernutrition and potential delayed cognitive development.[4-6] Thus, it is unclear whether the tested interventions were unable to improve cognition or whether the outcome measures lacked the sensitivity to detect changes in key measures. The current study focused on a single domain-general ability that broadly supports cognitive development throughout the lifespan – executive functions. Executive functions are a set of cognitive abilities that support goal-directed actions, planning, and problem solving and include working memory, cognitive flexibility (e.g., shifting action plans in response to environmental change), and inhibitory control (e.g., delay of gratification).[7] There is broad agreement that the emergence and development of executive function abilities early in development plays a critical role in longer-term academic and social competence across the lifespan.[8-12] For instance, individual differences in children's executive functions have been linked to developmental change in a broad range of cognitive and social processes in early childhood – including math and literacy ability,[10,11] theory of mind,[13,14] and emotion regulation[15] – as well as their academic and social competence later in adolescence.[12] In addition, deficits in executive function abilities are related to aspects of developmental delay.[16,17] Moreover, executive function abilities are present within the first year of life and have been shown to be stable even by early toddlerhood.[18] Finally, training programs specifically targeting executive function abilities in childhood have been shown to improve academic abilities such as reading[19] and arithmetic.[20] Given the emergence and stability of executive function early in development, its relation to many aspects of cognitive development, and the success of early interventions of executive function, it is recognized that focusing on interventions to improve executive functions early in development could have large and long-lasting impacts across the lifespan.[21,22]

In this study, our aim was to choose an executive function task that was developmentally appropriate across the full participant age range, could be administered easily by a local research team, and could be administered in a short time given the unfamiliarity of the local population with games and activities for young children. Although working memory, cognitive flexibility, and inhibitory control are all distinct executive functions, we focused specifically on children's working memory for three reasons. First, although all executive functions are related to intelligence, working memory abilities are most closely related to IQ scores, at least in adults.[23] Second, tasks used to assess cognitive flexibility and inhibitory control typically require verbal instructions and longer amounts of time than would be appropriate for all children in the study. Third, some of the tasks also include food components (e.g., delay of gratification), a factor that would be problematic to interpret in the context of a study in a low-income population, and would potentially have interfered with other outcome measures.

The specific task was a variant on the classic *Spin the Pots* task,[3,24,25] which assesses children's spatial working memory[24] and was previously adapted for local use and different ages.[3] Given the similarity to a hide-and-seek game, the task required no instructions and no verbal or written support for children to engage and succeed in the game. Moreover, the Spin the Pots task has been adapted previously in a study of children across a large age range who were also at risk for developmental delay.[25] Thus, the chosen task seemed very appropriate for use with the youngest 15-month-old children and oldest 7-year-old children, and sensitive enough to detect developmental change in our sample of children also at risk for delayed or impaired cognitive development.

Children were allowed to sit on a parent's knee if they wanted, and were presented with an array of small opaque cups, each covered by a lid with a distinct color and/or pattern, and were asked to find stickers that had

been hidden in the cups at the start of the test. The total number of cups depended on the age of the child (young children: 4 of 6 total cups; older children: 8 of 10 total cups). Repeat attempts to find stickers were conducted with the cups covered and rotated through 180° between tries as described in the main paper. The tests were continued until the child found all hidden stickers or they reached a predetermined set of trials (young children: 12 trials; older children: 18 trials). Performance was assessed by the total number of stickers found. The assessments followed a script developed by the lead psychologist (PM) and were administered in the local language in a quiet room in the village by a trained member of the research team. If a child became fussy or upset the assessment was stopped, and caregivers were told that they could stop the assessment at any time. All sessions were video-recorded for coding by trained staff at Tufts, and a log of stickers found was also kept by the local team. The Tufts coders were masked to randomization and used an established protocol.[3] A randomly selected subset of tests (n=20) was evaluated by all coders and inter-rater reliability was high (r >0.9). In addition, all video extractions were re-reviewed for quality control by a single supervisor (SFT). This follow-up revealed that protocol administration varied slightly for some children but was not different across groups.

Cerebral blood flow and cerebral oxygen metabolism. Cerebral blood flow is considered a sensitive marker of brain health throughout life because the human brain requires a constant movement of blood to deliver oxygen, glucose, and other essential nutrients, and remove carbon dioxide, lactic acid, and other metabolic products.[26]

To obtain a particularly robust and noninvasive index of cerebral blood flow (CBF_i) we combine NIRS with DCS. Numerous validation studies in humans and in animals have shown that CBF_i relative changes (obtained with DCS alone) and absolute values (obtained by correcting for tissue optical properties as measured by frequency- or time-domain NIRS) agree very well with cerebral blood flow values measured with "gold standard" methods, such as arterial spin-labeled MRI,[27] fluorescent microspheres,[28] bolus tracking time-domain NIRS[29] and phase-encoded velocity mapping MRI.[30] In addition, NIRS-DCS gives high test-retest in children living in low-resource settings.[31] The general principles of the methods and specifics of the system used in this study are described in the following paragraphs.

NIRS measurements quantify light attenuation, and from that estimates change in hemoglobin concentration (HbT), or cerebral blood volume, allowing for quantification of cerebral hemoglobin oxygenation (SO_2). NIRS SO_2 monitoring was introduced more than thirty years ago as a possible neonatal intensive care method[32] and FDA-cleared cerebral oximeters have been adopted by many hospitals worldwide. While SO_2 is often used as a surrogate for cerebral blood flow, hemoglobin oxygenation depends on both perfusion and consumption and cannot disentangle changes in flow and oxygen metabolism.[33-36] DCS was developed in the 1990s,[37,38] and, since then, has been widely adopted and is now being used in several clinical applications (see recent review papers[39-41]). DCS measures how fast coherent light loses coherence because of the movement of red blood cells. The correlation diffusion equation relates the motion of red blood cells in vessels to the temporal autocorrelation decay.[38,41] Since the correlation decay depends on both the speed of moving red blood cells in the media and on the number of scattering events with the moving particles, which depends on the area of the blood vessels, the slope of the correlation decay is proportional to actual blood flow and not simply flow velocity as in ultrasound methods. CBF_i (cm^2/s) is determined by fitting the correlation diffusion equation to the measured autocorrelation.

In this study a commercial NIRS-DCS system (MetaOx, ISS, Campaign, IL) was used to measure CBF_i, cm^2/s and oxygen metabolism ($CMRO_{2i}$).[40,42,43] This system integrates Frequency-Domain (FD) NIRS to measure HbT and SO_2, with DCS to measure CBF_i. The combination of hemoglobin oxygenation and CBF_i allow quantification of an index of cerebral oxygen metabolism ($CMRO_{2i}$), which, similarly to glucose metabolism, has been associated to brain development.[44,45] The details of the instrumentation and data analysis are reported elsewhere.[46]

Children were asked to sit still on a chair in a room with low light, and remain still for measurement, and could sit on a parent's knee if they wanted. A fiber optics monitor[46] was positioned on the forehead and held in place

by hand for 10s during data recording. We averaged 2 minutes per participant to measure 4 locations in the forehead (lower left and lower right over the Brodmann areas BA 10 and 46 [ventrolateral prefrontal cortex], and upper left and upper right over BA 9 [dorsolateral prefrontal cortex]). If the child moved during data acquisition or the detected light signal was low, measurements were repeated once. If the child appeared fussy or distressed he/she was not measured. For the FDNIRS data analysis we used four source-detector separation (1.5, 2, 2.5 and 3cm) and 7 wavelengths (690, 700, 730, 760, 780, 810 and 830nm). For the CBF_i estimates we used DCS data at 1.5cm source-detector separation to retain the largest number of measurements with adequate signal to noise ratio (SNR) and used the absorption and scattering coefficients simultaneously quantified by FDNIRS to account for differences between children. DCS data were also acquired at 0.5, 2.0 and 2.5cm and results at the larger separations (data not shown) were consistent with those observed at 1.5cm. For the $CMRO_{2i}$ estimates we used the DCS CBF_i and the FDNIRS SO_2 as in equation 1 of Dehaes et al.[47] and assumed a constant arterial oxygenation of 98% and a constant hemoglobin as these measures were only available on a subset of participants. While there were significant increases in hemoglobin in the blood with NEWSUP, we did not observe consistent increases in the subgroup measured with NIRS-DCS, suggesting that changes in hemoglobin did not play a substantial role in results observed for CBF_i and $CMRO_{2i}$.

Anemia. A lancet was used to obtain a drop of blood from the finger, which was wicked into a microcuvette for hemoglobin analysis with a standardized portable hemoglobinometer (Model 121721, Hemocue, Brea, CA).[48]

Anthropometry. Non-fasting weight was measured using a digital calibrated scale (±0.1kg, Floor Scale 813, Seca, Chino, CA). Height was assessed using an upright stadiometer (±0.1cm, Model 213, Seca). Mid-upper arm circumference (MUAC), head circumference, and bicep and triceps skinfold thicknesses at the MUAC site were measured ±0.1mm using paper tapes and calipers (Lange 85300, Beta Technology, Santa Cruz, CA).[49] All measures were taken in duplicate. Z-scores for weight-for-age (WAZ), height-for-age (HAZ) and body mass index (BMIZ) were calculated using WHO growth standards.[50,51] Data from 7 children with z-scores outside WHO standards (-6.0-5.0 for WAZ and BMIZ, -6.0-6 for HAZ[50]) were excluded from analyses. These children all had baseline HAZ values less than -6.0.

Body composition. A validated multi-compartment method was used, with lean tissue area and fat area calculated from MUAC and mean skinfolds.[52,53]

STATISTICAL ANALYSIS PLAN
[Changes after this plan were developed are indicated by square brackets and discussed on page 12.]

1. Overview

1.1. Background

Nearly half of children under the age of five who live in low-income countries fail to reach their developmental potential. Although inadequate diet is not the only underlying cause of developmental delay in children, more effective approaches to nutrition are recognized as essential to promote developmental milestones, particularly achieving optimal cognitive function. Stunting, anemia, and moderate-acute malnutrition also remain prevalent among young children around the globe, and are additionally associated with cognitive impairment. Limitations in attention span and working memory (and other measures of executive function), as well as reduced educational attainment later in life, have been consistently observed. Childhood undernutrition is associated with long-term impairments in cognition, and existing supplementary feeding programs have not demonstrated clear improvements. We aim to assess a novel food supplement (NEWSUP) for improving cognition and metabolic health in children at risk of undernutrition. A traditional fortified blended food (FBF) will also be evaluated. Both supplementary foods will be compared to a traditional breakfast meal (Control).

1.2. Objectives and hypotheses

We will assess the efficacy of a locally-prepared food for the prevention of malnutrition and stunting (NEWSUP) in comparison with 1) standard village practices (Control) and 2) a widely available FBF used by assistance programs. The supplement intervention will be implemented for 24 to 30 weeks. The primary outcome is change in executive function over the intervention period. The primary cohort of interest is the per-protocol cohort. The per-protocol cohort is defined as children with at least 75% adherence to supplementation.

Based on our previous pilot study,[3] we hypothesize that consumption of NEWSUP will be associated with improvements in cognition among children < 4 years of age (including all 3 year olds up to 3.9 years) compared to Controls. All analyses will therefore be conducted separately by child age group ($\leq$3.9 years and $\geq$4 years).

[See page 12 for discussions of the ITT analysis.]

2. Treatment interventions

2.1. Experimental group: locally-prepared bar

The NEWSUP is similar to the supplement recently tested during a previous pilot study. It is designed to facilitate growth and cognitive development. It will provide approximately 300 kcal per day, and will have approximately 20 to 30% of energy from protein (with 25 to 50% from an animal protein source), 20 to 35% of energy from carbohydrate, and 40 to 60% of energy from fat. The bar will be fortified with vitamins and minerals to meet USAID recommendations for moderate malnutrition and Dietary Reference Intake recommendations for at-risk and healthy children of the ages studied. It will contain a combination of local products and imported shelf-stable ingredients.

School children in first grade will receive their supplement on weekdays (Monday through Friday) in the morning before school starts. Younger children will receive the supplement on the same mornings at the community health center, distributed by community health workers. The teachers and community health workers will record amount of supplement consumption daily during the study, and will report the information weekly to the local research team throughout the intervention period.

[Community Health Workers subsequently modified the above plan slightly, to create three separate supplement centers within the villages, and provide all children with their randomized supplement at these sites.]

2.2. Active comparator: Fortified Blended Food (USAID Corn Soy Blend Plus)

The usual-intervention condition, FBF, will be approximately 300 kcal/day of USAID Corn Soy Blend Plus cooked in the usual manner with fortified vegetable oil and sugar (using a 10:3 ratio). The community health workers or other designated villagers will prepare the supplement freshly each intervention day using locally accepted standards for hygiene, and a quality control process for ratios of ingredients assigned by the research team to ensure consistent composition.

[Community Health Workers subsequently modified the above plan slightly, to create three separate supplement centers within the villages, and provide all children with their randomized supplement at these sites.]

School children in first grade will receive their supplement on weekdays (Monday through Friday) in the morning before school starts. Younger children will receive the supplement in the morning at the community health center, distributed by community health workers. The teachers and community health workers will record amount of supplement consumption daily during the study, and will report the information weekly to the local research team throughout the intervention period.

2.3. Placebo comparator: locally-purchased rice

The placebo Control condition will be approximately 300 kcal/day of locally-purchased rice cooked with a small amount of oil (10:2 ratio), which represents the usual breakfast of children in this region. The community health workers or other designated villagers will prepare the rice freshly each intervention day using locally accepted standards for hygiene, and a quality control process for ratios of ingredients assigned by the research team to ensure consistent composition.

School children in first grade will receive their supplement on weekdays (Monday through Friday) in the morning before school starts. Younger children will receive the supplement in the morning at the community health center, distributed by community health workers. The teachers and community health workers will record amount of supplement consumption daily during the study, and will report the information weekly to the local research team throughout the intervention period.

[Community Health Workers subsequently modified the above plan slightly, to create three separate supplement centers within the villages, and provide all children with their randomized supplement at these sites.]

3. Eligibility criteria

3.1. Village inclusion criteria

- Between 8 to 12 villages in the Oio and Cacheu regions of Guinea-Bissau, to provide the estimated number of subjects, will be recruited for inclusion in this study.
- Villages will be selected based on a convenience sample chosen from villages based on the network of our locally-based research partner (IPHD; International Partnership for Human Development).

3.2. Participant inclusion criteria

- Non-malnourished children are eligible to participate in this study if they meet the subsequent inclusion criteria.
- Children are eligible for the study if a parent or legal guardian provides written informed consent for enrollment.

- Children ages 15 months to seven years are considered eligible.
- Male and female children are eligible for enrollment.
- Children are eligible if the family plans to remain in the village for the duration of the study (up to 30 weeks) based on self-reported intention by the parent.
- Children are eligible if they have no known food allergies self-reported by the parent or guardian.

3.3. Participant exclusion criteria

If a child is identified as malnourished at baseline, the child will be considered ineligible for enrollment and will be excluded from the study due to malnutrition. The parent or guardian will be advised to take the child to the nearest malnutrition clinic. Malnutrition will be defined as a mid-upper arm circumference in the red zone of the paper tape.

4. Withdrawal and termination criteria

Children who experience any severe adverse event as outlined in the study protocol will be withdrawn from the study. If a community health worker suspects an adverse reaction to the supplement, the child and his or her parent/legal guardian will be withdrawn from the study. Participants may withdraw their consent at any time. Each prospective family is assured that they need not participate and may change their mind at any time.

5. Randomization and concealment

This is a within-village randomization and the family is considered the unit of randomization. Villagers will be informed of the randomization after the completion of baseline testing. All children will receive a dietary intervention. This is a parallel-assignment intervention model with three arms, including: 1) experimental NEWSUP arm (locally-prepared paste); 2) active FBF comparator (USAID Corn Soy Blend Plus); and 3) placebo comparator (Control, locally-purchased rice).

We have 3 levels of staff for our projects in Guinea-Bissau: a) Tufts researchers, b) the Bissau research team (3 full-time senior research coordinators, and 16 per diem outcomes staff), and c) 90 village research assistants (3 teams of 3 individuals per village), and our method is as follows:

Allocation concealment is assured by a separate team (the local Bissau researchers) assigning family IDs in numerical order as families are enrolled within villages. There is no randomization at this stage and local researchers do not have any access to the randomization codes. Enrollment takes 1-3 days per village, and a day or two later the assigned family IDs are matched to their randomization by the Tufts researchers and lists are generated for families in each treatment. This list is shared with the Bissau researchers for implementation by the village research teams.

[Note: enrollment in this study includes both screening and baseline outcomes.]

Tufts researchers (who do not know the local families) will generate a randomized list assigning IDs within villages to the 3 treatment groups prior to traveling to Guinea-Bissau to launch the study, and the number of family numbers generated for each village is based on projected enrollment numbers plus an allowance for unanticipated families. Randomization will be conducted at Tufts University by a coordinator blinded to the baseline child characteristics. Randomization will be performed at the level of the family using a random number generator, and sampling will be performed without replacement using a random seed. At no point will there be any deviation from the assigned randomization. This list generation is done in advance because sometimes the internet goes down in Bissau so we cannot rely on doing it in situ.

The randomization lists are shared with the village research assistants who prepare the supplement when the supplementation starts (3 separate locations/village). After the first day of supplementation the children know where to go, and checklists are used by the village research assistants to record attendance and consumption. Quality control is assured during the course of the study by the Bissau researchers coming to the village twice weekly to check on preparation and consumption and study records, and by Tufts researchers providing additional oversight at intervals. The village teams also keeps a photographic record that supplement is prepared and distributed on other days.

6. Sample size calculation

Based on our recent pilot study, we conservatively calculated that we will have 80% power to detect a difference in cognition between treatments of 50% of the difference seen in the pilot between the intervention and assessment-only control groups with 900 children.

Sample sizes were calculated with 80% power to detect half the effect size observed in the pilot (n=80 per arm; mean difference = 0.28 stickers compared to 0.56 stickers found in the pilot). Target enrollment was n=150 per arm in each age group (total 900 children) to account for potential 25% attrition and potential family clustering within age-groups to ensure sufficient power to detect an effect on the primary outcome. The original sample size calculation did not formally account for clustering of children within families. However, a post-hoc calculation using the mean family size (n=2 children) and the observed ICC for the primary outcome (ICC = 0.01 for cognition) was performed. A design effect = 1.01 and an effective sample size of n = 1048 for this study was observed, indicating that our enrolled sample (n=1059) is sufficient to detect the intended mean difference in working memory.

Note: A total of 1059 children completed baseline assessments. During enrollment it was necessary to enroll all children in the target villages (because to turn away eligible children would be culturally unacceptable) and therefore an amendment was submitted to the IRB after completion of baseline enrollment, to request use of data from the additional enrollees (which was granted).

7. Analytical approach

7.1. Per-protocol analysis

The primary method of analysis will be a per-protocol analysis. The per-protocol cohort will include participants who consumed at least 75% of their supplement over the duration of the intervention. The per-protocol analysis will compare the effect of the locally-prepared bar and the active comparator to the placebo group.

7.2. Intention-to-treat analysis

The secondary method of analysis will be an intention-to-treat (ITT) analysis. The ITT cohort will include all possible participants who enrolled in the study and were randomized, regardless of supplement consumption. The ITT analysis will compare the effect of the locally-prepared bar and the active comparator to the placebo group.

[See page 12 for discussions of the per-protocol and ITT analyses.]

7.3. Post-hoc comparisons

The effect of the locally-prepared bar and the active comparator will be compared in a post-hoc analysis. Post-hoc comparisons will be made for all primary and secondary outcomes. These analyses will be considered exploratory as this study is not powered to detect a difference between the locally-prepared bar (NEWSUP) and the active comparator group (FBF). An exploratory analysis of effect modification of supplementation by child age group was also conducted.

7.4. Other

- Participants without follow-up data for a specific outcome variable will be excluded from all related analyses for the per-protocol and ITT cohorts.
- Missing data at follow-up will not be imputed as measurements will only be obtained at two time points (baseline and follow-up).
- Adjustment for multiple comparisons will not be applied. Only one comparison will be made for the primary outcome. All analyses of secondary outcomes and all post-hoc comparisons between NEWSUP and FBF will be considered exploratory.
- A *P* value less than 0.05 will be considered statistically significant. All significance levels will be two-sided.

8. Outcomes

8.1. Primary outcome

The primary outcome was determined *a priori* as the change in cognitive function over the intervention period for children randomized to receive the locally-prepared bar (NEWSUP) versus the Control. The primary population of interest is children up to three years of age (including up to 3.9 years). Executive function was assessed by a variation on the classic *Spin the Pots* test.[24,25] This assessment method was previously adapted for local use.

Briefly, children were presented with an array of small opaque cups, each covered by a lid with a distinct color or pattern. Children were asked to find the stickers that had been hidden in the cups at the beginning of the test. The total number of cups was dependent on the age of the child (children under four years: 4 of 6 total cups; children four years and older: 8 of 10 total cups). Repeated attempts to find stickers were conducted with the cups covered. The cups were rotated 180° between tries. The tests were continued until the child found all hidden stickers or until they reached a predetermined set of trials (children under four years: 12 trials; children four years and older: 18 trials). The outcome of interest is a change in the number of stickers found over the intervention period.

8.2. Secondary outcomes

8.2.1. Measures of growth

- Changes in weight-for-age, height-for age, and body mass index (BMI)-for-age z-scores. All z-scores will be calculated based on age- and sex-specific growth standards provided by the World Health Organization (WHO).
- Changes in lean tissue accretion will be calculated based on measures of mid-upper arm circumference and biceps and triceps skinfolds.[52,54]
- Changes in hemoglobin levels. The presence of anemia and level of severity will be assessed based on age- and sex-specific WHO classifications.

8.2.2. Measures of cerebral hemodynamics

- As measured by a commercial near infrared spectroscopy and diffuse correlation spectroscopy (NIRS-DCS) system (6):
    - Cerebral blood flow and rate of cerebral oxygen metabolism
    - Hemoglobin concentration
    - Hemoglobin oxygenation

9. Variables

9.1. Intervention attendance

All supplements will be served as a supervised breakfast on weekdays (five days per week, Monday through Friday) by trained villagers with no role in the study design or outcome measurements. Child attendance (present or absent) and consumption (0%, 25%, 50%, 75%, and 100%) will be recorded each weekday for the duration of the intervention.

Weekly adherence to supplementation will be calculated by taking the sum of the consumption (between 0 and 1 for each day) and dividing by the number of weekdays. Overall adherence to supplementation will be calculated based on the quantity of supplement consumed over the duration of the study (sum of weekly consumption divided by the number of intervention weeks). Participants with overall adherence equivalent to at least 75% consumption will be included in the per-protocol analysis.

9.2. Demographic (collected at baseline and post-intervention)

- Age
- Sex
- Village
- Region
- Study cohort (to account for potential seasonal differences on the collected data)

9.3. Cognitive (collected at baseline and post-intervention)

- Number of stickers hidden
- Number of stickers found
- Number of attempts given

9.4. Anthropometry and health measures (collected at baseline and post-intervention)

- Weight (kg)
- Height (cm)
- Mid-upper arm circumference (cm)
- Bicep skinfold (cm)
- Triceps skinfold (cm)
- Head circumference (cm)
- Hemoglobin (g/dL)

9.5. Cerebral hemodynamics (collected at baseline and post-intervention)

- Cerebral oxygen metabolism (au)
- Cerebral blood flow ($mm^2/s\ x10^{-8}$)
- Hemoglobin concentration (µM)
- Hemoglobin oxygenation (%)

10. Summary of pre-intervention characteristics

Pre-intervention characteristics by child age group (≤ 3.9 years, > 4 years) will be compared for the three randomized groups for the per-protocol and the ITT cohorts. Variables that are different between the three groups at baseline will be considered as potential covariates in the multivariable models outlined below.

11. Outliers and assumptions of statistical tests

Data will be assessed graphically for the presence of outliers. Participants with biologically implausible measurements for calculated WAZ, HAZ, and BMIZ at baseline based on WHO standards will be excluded from all analyses (-6.0 to 5.0 for WAZ and BMIZ, -6.0 to 6.0 for HAZ).[50]

The assumptions for multivariable linear mixed models will be verified, including normality of the residuals of the primary and secondary outcome variables. Violation of the model assumptions for linear regression will be addressed through variable transformation as appropriate.

12. Statistical analysis

The primary outcome will be assessed as the discrete number of stickers found at follow-up using a multivariable Poisson model, with the natural log of the total number of searches given included as an offset. Changes in each secondary outcome as reported above will be assessed by multivariable linear mixed regression models. All analyses will be applied separately for children ≤ 3.9 years and children ≥ 4 years, and ≤ 3.9 years is the primary age group of interest. All models will account for the cluster-randomization at the level of the family as a random effect. Models will be adjusted for age, sex, baseline measurement, and study cohort. Additional covariates will be included as appropriate based on differences between the three randomized groups at baseline.

[See page 12 for rationale for the change to a Poisson model during statistical review of the manuscript.]

The primary comparison of interest is for NEWSUP and FBF versus the Control group. Pairwise comparisons between the locally-prepared bar and the active comparator will be performed. Identical methods will be employed for the analysis of the per-protocol and ITT cohorts. The potential interaction between supplement group and child age group on changes in a primary or secondary outcome will be evaluated by including an interaction term for supplement * age group in a model including all children.

Participants with implausible values at baseline will be excluded from the analyses. All analyses were performed using SAS version 9.4. A *P* value <0·05 will be considered statistically significant.

Summary of changes to the statistical analysis plan

1. The preplanned primary method of analysis was a per-protocol analysis (predefined as children consuming ≥75% of their supplement) because our intention was to look at the efficacy of the supplement if consumed. This analysis is outlined in the statistical analysis plan, above, that was developed prior to receipt of the data or any data analysis. However, a clerical error in the clinical trial registration (clinicaltrials.gov; NCT 03017209) did not describe this predetermined population focus specifically, and the registration implied an ITT analysis by default. The analytical approach was therefore subsequently revised to designate the intention-to-treat cohort as the primary cohort of interest and secondary analyses included the per-protocol cohort.

2. It was also deemed necessary to determine whether the cognitive improvements observed among children under age four was confounded by the difficulty of the test. Based on the recommendation of the statistical reviewer, the modeling approach for the primary outcome was changed from a linear mixed model that used the change in z-scores as the outcome to a Poisson regression model in which number of stickers is treated as an integer. The Poisson model includes an offset for the number of trials allotted to each child.

3. Examination of the baseline data indicated differences in mean hemoglobin between groups in the children 15 months to 3.9 years, due to differences in the number of severely anemic children. In addition, a model of baseline cognition revealed that baseline WAZ was a significant predictor of cognition. We therefore included baseline and six-month changes in both WAZ and hemoglobin measurements as covariates in fully adjusted models predicting cognition. Models included or did not include these variables to address the question of potentially different effects of the supplements on growth, and both included or did not include severely anemic children as a way to further address the uneven distribution of anemia across groups.

Supplementary Table A. Baseline nutritional benchmarks for children in three randomized groups in rural Guinea-Bissau.

	Intention-to-treat population				Per-protocol population			
	NEWSUP	**FBF**	**Control**		**NEWSUP**	**FBF**	**Control**	
Children ≤ 3.9 years	n (%) [1]	n (%)	n (%)	***P* value**[2]	n (%) [1]	n (%)	n (%)	***P* value**[3]
Anthropometry	**n=157**	**n=141**	**n=135**		**n=119**	**n=106**	**n=107**	
Weight for age z-score < - 2	35 (22.3)	33 (23.4)	37 (27.4)	0.57	24 (20.2)	25 (23.6)	30 (28.0)	0.38
Height for age z-score < -2	70 (44.6)	56 (39.7)	63 (46.7)	0.49	48 (40.3)	44 (41.5)	47 (43.9)	0.86
BMI for age z-score < -2	6 (3.8)	3 (2.1)	8 (5.9)	0.27	6 (5.0)	2 (1.9)	7 (6.5)	0.25
Hemoglobin	**n=113**	**n=111**	**n=103**		**n=83**	**n=80**	**n=76**	
Presence of anemia (%)	75 (66.4)	95 (85.6)	77 (74.8)	0.003	57 (68.7)	67 (83.8)	55 (72.4)	0.06
Children with ≥ 1 poor nutritional benchmark (%)[2]	94 (59.9)	94 (66.7)	86 (63.7)	0.47	70 (58.8)	67 (63.2)	66 (61.7)	0.79
Children ≥ 4 years								
Anthropometry	**n=202**	**n=207**	**n=209**		**n=176**	**n=175**	**n=178**	
Weight for age z-score < - 2	49 (24.3)	55 (26.6)	53 (25.4)	0.87	42 (23.9)	48 (27.4)	46 (25.8)	0.75
Height for age z-score < -2	48 (23.8)	50 (24.2)	45 (21.5)	0.79	41 (23.3)	44 (25.1)	41 (23.0)	0.88
BMI for age z-score < -2	16 (7.9)	19 (9.2)	21 (10.1)	0.75	12 (6.8)	16 (9.1)	19 (10.7)	0.44
Hemoglobin	n=142	n=145	n=148		n=117	n=117	n=121	
Presence of anemia (%)	100 (70.4)	102 (70.3)	104 (70.3)	>0.99	83 (70.9)	82 (70.1)	78 (64.5)	0.52
Children with ≥ 1 poor nutritional benchmark (%)[2]	112 (55.5)	125 (60.4)	128 (61.2)	0.44	96 (54.6)	104 (59.4)	104 (58.4)	0.62

BMI, body mass index; CI, confidence interval; FBF, fortified blended food; MUAC, mid-upper arm circumference; NEWSUP, New Supplement.

[1]Categorical data presented as n (%).

[2]For comparisons between three randomized groups in the ITT cohort, calculated by linear mixed models.

[3]For comparisons between three randomized groups in the PP cohort, calculated by linear mixed models.

[4]Defined as having at least one of the following: weight, height, or BMI z-score below -2, the presence of moderate or severe anemia.

Supplementary Table B. Baseline demographic, cognitive, and anthropometric characteristics of children in three randomized groups in the per-protocol population in rural Guinea-Bissau.

	NEWSUP	**FBF**	**Control**	
Children ≤ 3.9 years	Mean (95% CI) [1]	Mean (95% CI)	Mean (95% CI)	***P* value**[2]
Demographic	**n=119**	**n=106**	**n=107**	
Age (years)	3.0 (2.8, 3.1)	2.9 (2.7, 3.0)	2.9 (2.7, 3.0)	0.63
Sex				
Male	63 (52.9)	55 (51.9)	65 (60.8)	0.36
Female	56 (47.1)	51 (48.1)	42 (39.3)	
Anthropometry	**n=119**	**n=106**	**n=107**	
Weight for age (Z-score)	-1.3 (-1.5, -1.0)	-1.3 (-1.5, -1.0)	-1.4 (-1.6, -1.1)	0.71
Height for age (Z-score)	-1.7 (-2.0, -1.5)	-1.7 (-2.0, -1.4)	-1.8 (-2.1, -1.5)	0.86
BMI for age (Z-score)	-0.3 (-0.5, -0.1)	-0.2 (-0.4, 0.02)	-0.3 (-0.5, -0.1)	0.84
MUAC (cm)	15.6 (15.3, 15.8)	15.6 (15.4, 15.8)	15.5 (15.3, 15.7)	0.89
Lean tissue area (cm^2)	14.7 (12.1, 17.2)	13.4 (10.7, 16.1)	13.9 (11.2, 16.6)	0.80
Fat tissue area (cm^2)	178.8 (172.9, 184.6)	181.3 (175.1, 187.5)	178.9 (172.7, 185.0)	0.81
Cognitive	**n=81**	**n=65**	**n=66**	
Stickers hidden	6.0 (5.5, 6.5)	5.7 (5.1, 6.2)	6.1 (5.5, 6.6)	0.50
Searches offered	8.6 (8.1, 9.1)	8.3 (7.7, 8.8)	8.6 (8.0, 9.1)	0.60
Stickers found	3.5 (3.1, 3.9)	3.4 (3.0, 3.9)	3.2 (2.8, 3.6)	0.44
Hemoglobin	**n=83**	**n=80**	**n=76**	
Hemoglobin (g/dL)	10.3 (10.0, 10.6)	9.7 (9.4, 10.1)	10.0 (9.7, 10.3)	0.06
Anemia classification (%)				
Normal	26 (31.3)	13 (16.3)	21 (27.6)	0.37
Mild	25 (30.1)	26 (32.5)	21 (27.6)	
Moderate	32 (38.6)	36 (45.0)	33 (43.4)	
Severe	0 (0.0)	5 (6.3)	1 (1.3)	
Children ≥ 4 years				
Demographic	**n=176**	**n=175**	**n=178**	
Age	6.0 (5.8, 6.2)	5.9 (5.7, 6.0)	5.9 (5.7, 6.0)	0.33
Sex				
Male	97 (55.1)	85 (48.6)	90 (50.6)	0.45
Female	79 (44.9)	90 (51.4)	88 (49.4)	
Anthropometry	**n=176**	**n=175**	**n=178**	
Weight for age (Z-score)	-1.4 (-1.5, -1.2)	-1.4 (-1.6, -1.3)	-1.4 (-1.6, -1.3)	0.86
Height for age (Z-score)	-1.3 (-1.5, -1.1)	-1.3 (-1.5, -1.1)	-1.3 (-1.5, -1.1)	0.98
BMI for age (Z-score)	-0.8 (0.9, -0.7)	-0.9 (-1.0, -0.7)	-0.8 (-1.0, -0.7)	0.83
MUAC (cm)	16.3 (16.1, 16.5)	16.2 (16.0, 16.4)	16.2 (16.0, 16.4)	0.54
Lean tissue area (cm^2)	37.3 (33.1, 41.4)	33.2 (29.0, 37.3)	36.5 (32.4, 40.6)	0.34
Fat tissue area (cm^2)	175.8 (170.6, 181.0)	176.8 (171.6, 182.0)	173.1 (168.0, 178.3)	0.59
Cognitive	**n=141**	**n=149**	**n=134**	
Stickers hidden	8.0 (7.9, 8.0)	7.9 (7.9, 8.0)	8.0 (7.9, 8.0)	0.59
Searches given	10.1 (9.9, 10.2)	10.1 (9.9, 10.2)	9.9 (9.8, 10.0)	0.14
Stickers found	5.3 (5.0, 5.5)	5.3 (5.1, 5.5)	5.3 (5.1, 5.5)	0.99
Hemoglobin	**n=117**	**n=117**	**n=121**	
Hemoglobin (g/dL)	10.5 (10.1, 10.8)	10.4 (10.1, 10.7)	10.5 (10.2, 10.9)	0.87
Anemia classification (%)				
Normal	34 (29.1)	35 (29.9)	43 (35.5)	0.34
Mild	20 (17.1)	20 (17.1)	19 (15.7)	
Moderate	58 (49.6)	55 (47.0)	54 (44.6)	
Severe	5 (4.3)	7 (6.0)	5 (4.1)	

BMI, body mass index; CI, confidence interval; FBF, fortified blended food; MUAC, mid-upper arm circumference; NEWSUP, New Supplement.

[1]Continuous data presented as cluster-adjusted means (95% CIs); categorical data presented as n (%).

[2]For comparisons between three randomized groups in the per-protocol population, calculated by linear mixed models for continuous variables and the Chi-square test for categorical variables.

Supplementary Table C. Baseline demographic and anthropometric measurements in the three randomized groups of children by adherence to supplementation in rural Guinea Bissau.

	NEWSUP[1]		FBF		Control		*P* value[2]
	< 75% adherence n=64	≥ 75% adherence n=295	< 75% adherence n=67	≥ 75% adherence n=281	< 75% adherence n=59	≥ 75% adherence n=285	
Demographic							
Age (years)	3.8 (3.4, 4.3)	4.8 (4.6, 5.0)	3.9 (3.5, 4.4)	4.7 (4.5, 4.9)	4.3 (3.8, 4.7)	4.7 (4.5, 4.9)	<0.001
Sex							
Male	27 (42.2)	160 (54.2)	33 (49.3)	140 (49.8)	39 (66.1)	155 (54.5)	0.85
Female	37 (57.8)	135 (45.8)	34 (50.8)	141 (50.2)	20 (33.9)	130 (45.6)	
Adherence to supplement (%)	48.6 (45.4, 51.7)	91.1 (89.2, 92.9)	40.2 (37.0, 43.4)	91.3 (89.6, 93.1)	41.1 (37.6, 44.7)	92.8 (91.0, 94.5)	--
Children per father	1.7 (1.5, 2.0)	2.5 (2.4, 2.6)	1.8 (1.5, 2.0)	2.3 (2.2, 2.4)	1.9 (1.7, 2.2)	2.3 (2.1, 2.4)	<0.001
Anthropometry							
Weight for age (Z-score)	-1.5 (-1.7, -1.2)	-1.3 (-1.5, -1.2)	-1.3 (-1.6, -1.1)	-1.4 (-1.5, -1.2)	-1.4 (-1.6, -1.1)	-1.4 (-1.5, -1.3)	0.96
Height for age (Z-score)	-1.8 (-2.1, -1.5)	-1.5 (-1.6, -1.3)	-1.6 (-1.9, -1.3)	-1.5 (-1.6, -1.3)	-1.6 (-1.9, -1.3)	-1.5 (-1.6, -1.3)	0.45
BMI for age (Z-score)	-0.5 (-0.7, 0.2)	-0.6 (-0.7, -0.5)	-0.5 (-0.7, -0.2)	-0.6 (-0.7, -0.5)	-0.5 (-0.8, -0.3)	-0.6 (-0.7, -0.5)	0.85
MUAC (cm)	15.6 (15.3, 15.9)	16.0 (15.9, 16.2)	15.8 (15.5, 16.1)	16.0 (15.8, 16.1)	15.6 (15.3, 15.9)	15.9 (15.8, 16.1)	0.09
Anemia classification (%)							
Normal	20 (36.4)	60 (30.0)	11 (18.6)	48 (24.4)	6 (11.1)	64 (32.5)	0.04
Mild	13 (23.6)	45 (22.5)	10 (17.0)	46 (23.4)	13 (24.1)	40 (20.3)	
Moderate	21 (38.2)	90 (45.0)	34 (57.6)	91 (46.2)	30 (55.6)	87 (44.2)	
Severe	1 (1.8)	5 (2.5)	4 (6.8)	12 (6.1)	5 (9.3)	6 (3.1)	

[1]Continuous data presented as cluster-adjusted means (95% CIs); categorical data presented by n (%).
[2]*P* values for baseline differences between < 75% adherence and ≥ 75% adherence (combining the three randomized groups) calculated by linear mixed models for continuous variables and Chi-square for categorical variables. Mantel-Haenszel *P* value reported for baseline anemia classification.

Supplementary Table D. Multivariable Poisson models predicting changes in cognition: an exploratory analysis of effect modification between supplementation and age group.

	Model 1[1]		Model 2[2]		Model 1[3]		Model 2[4]	
	Adjusted rate ratio (95% CI)	***P* value**	**Adjusted rate ratio (95% CI)**	***P* value**	**Adjusted rate ratio (95% CI)**	***P* value**	**Adjusted rate ratio (95% CI)**	***P* value**
Intention-to-treat cohort								
Children ≤3.9 years								
Control	*Referent*		*Referent*		*Referent*		*Referent*	
FBF	1.08 (0.93, 1.26)	0.33	1.06 (0.89, 1.28)	0.51	1.07 (0.92, 1.26)	0.38	1.05 (0.87, 1.27)	0.60
NEWSUP	1.16 (1.02, 1.31)	0.02	1.16 (1.00, 1.36)	0.05	1.16 (1.02, 1.31)	0.02	1.16 (1.00, 1.36)	0.05
Children ≥4 years								
Control	*Referent*		*Referent*		*Referent*		*Referent*	
FBF	1.07 (1.01, 1.13)	0.03	1.06 (0.99, 1.14)	0.09	1.05 (0.99, 1.12)	0.09	1.05 (0.98, 1.14)	0.19
NEWSUP	1.03 (0.97, 1.10)	0.33	1.02 (0.95, 1.10)	0.59	1.02 (0.96, 1.09)	0.47	1.02 (0.94, 1.10)	0.68
***P* interaction (group * age group)**	0.22		0.29		0.21		0.21	
Per-protocol cohort								
Children ≤3.9 years								
Control	*Referent*		*Referent*		*Referent*		*Referent*	
FBF	1.07 (0.91, 1.26)	0.41	1.05 (0.87, 1.28)	0.61	1.06 (0.90, 1.26)	0.48	1.04 (0.85, 1.27)	0.72
NEWSUP	1.18 (1.03, 1.35)	0.02	1.21 (1.03, 1.41)	0.02	1.18 (1.03, 1.35)	0.02	1.21 (1.03, 1.41)	0.02
Children ≥4 years								
Control	*Referent*		*Referent*		*Referent*		*Referent*	
FBF	1.06 (1.00, 1.13)	0.06	1.07 (0.99, 1.16)	0.08	1.05 (0.98, 1.12)	0.14	1.07 (0.98, 1.16)	0.12
NEWSUP	1.03 (0.96, 1.10)	0.44	1.02 (0.94, 1.11)	0.62	1.02 (0.95, 1.10)	0.54	1.02 (0.94, 1.12)	0.62
***P* interaction (group * age group)**	0.15		0.09		0.15		0.09	

CI, confidence interval; FBF, fortified blended food; NEWSUP, New Supplement.

[1] Model 1: calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline cognitive function, and the interaction between treatment group and age group. The natural logarithm of the total number of searches given is included as an offset.

[2] Model 2: calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline cognitive function, baseline WAZ, baseline hemoglobin (g/dL), change in WAZ, change in hemoglobin, and the interaction between treatment group and age group. The natural logarithm of the total number of searches given is included as an offset.

[3] Model 1 (excludes participants with severe anemia at baseline): calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline cognitive function, and the interaction between treatment group and age group. The natural logarithm of the total number of searches given is included as an offset.

[4] Model 2 (excludes participants with severe anemia at baseline): calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline cognitive function, baseline WAZ, baseline hemoglobin (g/dL), change in WAZ, change in hemoglobin, and the interaction between treatment group and age group. The natural logarithm of the total number of searches given is included as an offset.

Supplementary Table E. Baseline measurements of cerebral blood flow and oxygen metabolism in four regions of the brain in the intention-to-treat and per-protocol populations in rural Guinea-Bissau.

	NEWSUP		FBF		Control	
	ITT cohort	**PP cohort**	**ITT cohort**	**PP cohort**	**ITT cohort**	**PP cohort**
	Mean (95% CI)[1]	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)[1]	Mean (95% CI)	Mean (95% CI)
Demographic						
Age	4.1 (3.6, 4.5)	4.1 (3.7, 4.5)	4.6 (4.2, 5.0)	4.7 (4.3, 5.1)	4.5 (4.1, 4.9)	4.5 (4.1, 4.9)
Sex						
Male	26 (52.0)	26 (53.1)	24 (47.1)	22 (45.8)	31 (58.5)	29 (59.2)
Female	24 (48.0)	23 (46.9)	27 (52.9)	26 (54.2)	22 (41.5)	20 (40.8)
NIRS DCS measurements						
Left ventrolateral prefrontal cortex	**n=38**	**n=37**	**n=43**	**n=41**	**n=41**	**n=37**
Cerebral blood flow index (mm^2/s $x10^{-8}$)	3.0 (2.3, 3.8)	3.0 (2.2, 3.8)	3.5 (2.8, 4.2)	3.4 (2.6, 4.1)	3.1 (2.4, 3.8)	3.1 (2.3, 3.9)
Cerebral oxygen metabolism index (au)	10.1 (7.4, 12.7)	10.1 (7.3, 12.8)	11.5 (9.0, 14.0)	11.1 (8.5, 13.7)	10.5 (8.0, 13.1)	10.6 (7.9, 13.4)
Hemoglobin concentration (μM)	64.8 (60.6, 68.9)	64.4 (60.0, 68.8)	67.5 (63.6, 71.4)	67.5 (63.4, 71.7)	57.8 (53.8, 61.8)	58.4 (54.0, 62.8)
Hemoglobin oxygenation (%)	64.4 (62.6, 66.3)	64.6 (62.7, 66.4)	65.4 (63.6, 67.1)	65.7 (63.9, 67.4)	63.8 (62.0, 65.6)	64.0 (62.1, 65.8)
Right ventrolateral prefrontal cortex	**n=38**	**n=38**	**n=40**	**n=37**	**n=41**	**n=37**
Cerebral blood flow index (mm^2/s $x10^{-8}$)	1.6 (1.2, 2.0)	1.6 (1.1, 2.0)	1.9 (1.5, 2.3)	2.0 (1.5, 2.4)	1.6 (1.2, 2.0)	1.6 (1.2, 2.1)
Cerebral oxygen metabolism index (au)	5.5 (4.0, 7.1)	5.5 (4.0, 7.1)	6.6 (5.1, 8.1)	6.7 (5.1, 8.3)	5.8 (4.3, 7.2)	6.0 (4.4, 7.5)
Hemoglobin concentration (μM)	80.7 (76.7, 84.7)	80.6 (76.6, 84.6)	76.8 (72.9, 80.8)	77.4 (73.3, 81.5)	76.7 (72.7, 80.6)	77.4 (73.2, 81.6)
Hemoglobin oxygenation (%)	62.3 (60.6, 64.0)	62.4 (60.6, 64.0)	63.5 (61.9, 65.2)	63.9 (62.2, 65.6)	61.7 (60.0, 63.3)	61.9 (60.2, 63.6)
Left dorsolateral prefrontal cortex	**n=37**	**n=36**	**n=42**	**n=39**	**n=40**	**n=37**
Cerebral blood flow index (mm^2/s $x10^{-8}$)	4.0 (3.1, 4.8)	3.9 (3.0, 4.7)	4.9 (4.1, 5.7)	5.0 (4.2, 5.8)	4.0 (3.2, 4.9)	4.1 (3.2, 4.9)
Cerebral oxygen metabolism index (au)	13.9 (10.9, 16.8)	13.5 (10.6, 16.4)	15.9 (13.1, 18.7)	16.1 (13.3, 18.8)	13.4 (10.5, 16.2)	13.3 (10.4, 16.1)
Hemoglobin concentration (μM)	69.2 (64.3, 74.1)	69.4 (64.4, 74.4)	66.9 (62.3, 71.6)	67.0 (62.1, 71.8)	69.2 (64.5, 74.0)	70.1 (65.1, 75.0)
Hemoglobin oxygenation (%)	63.7 (61.8, 65.6)	64.0 (62.1, 65.9)	65.1 (63.3, 66.9)	65.5 (63.7, 67.3)	64.4 (62.5, 66.2)	64.9 (63.0, 66.7)
Right dorsolateral prefrontal cortex	**n=39**	**n=38**	**n=41**	**n=39**	**n=45**	**n=41**
Cerebral blood flow index (mm^2/s $x10^{-8}$)	3.3 (2.7, 3.9)	3.2 (2.6, 3.8)	3.3 (2.7, 3.9)	3.2 (2.6, 3.8)	2.6 (2.0, 3.2)	2.6 (2.0, 3.2)
Cerebral oxygen metabolism index (au)	12.9 (10.5, 15.3)	12.5 (10.1, 14.8)	11.8 (9.4, 14.1)	11.3 (9.0, 13.7)	10.1 (7.9, 12.3)	10.1 (7.8, 12.4)
Hemoglobin concentration (μM)	64.5 (61.4, 67.6)	64.7 (61.6, 67.7)	68.6 (65.6, 71.7)	69.3 (66.3, 72.4)	66.9 (64.1, 69.8)	67.2 (64.2, 70.2)
Hemoglobin oxygenation (%)	59.1 (57.4, 60.7)	59.2 (57.5, 60.8)	61.7 (60.1, 63.3)	62.1 (60.5, 63.8)	59.7 (58.2, 61.3)	59.9 (58.3, 61.5)

CI, confidence interval; FBF, fortified blended food; ITT, intention-to-treat; NEWSUP, New Supplement; PP, per-protocol.
[1]Continuous data presented as cluster-adjusted means (95% CIs).

Supplementary Table F. Multivariable linear mixed models predicting 6-month changes in cerebral hemodynamics in the four regions of the brain in the intention-to-treat and per-protocol cohorts in rural Guinea Bissau.

	NEWSUP		FBF		
	Adjusted mean difference (95% CI)[1]	***P* value[2]**	**Adjusted mean difference (95% CI)[1]**	***P* value[3]**	***P* value[4]**
Intention-to-treat cohort					
Left ventrolateral prefrontal cortex (n=122)					
Cerebral blood flow index (mm^2/s x10^{-8})	1.14 (0.10, 2.23)	0.04	0.003 (-1.10, 1.10)	0.99	0.04
Cerebral oxygen metabolism index (au)	4.54 (0.64, 8.44)	0.02	-0.10 (-3.89, 3.75)	0.98	0.02
Hemoglobin concentration (µM)	-1.02 (-5.57, 3.53)	0.66	-1.46 (-6.02, 3.11)	0.53	0.85
Hemoglobin oxygenation (%)	-1.87 (-3.57, -0.18)	0.03	-0.14 (-1.82, 1.53)	0.86	0.04
Right ventrolateral prefrontal cortex (n=119)					
Cerebral blood flow index (mm^2/s x10^{-8})	0.57 (-0.29, 1.44)	0.19	-0.11 (-0.98, 0.76)	0.81	0.12
Cerebral oxygen metabolism index (au)	1.99 (-1.10, 5.10)	0.20	-0.52 (-3.60, 2.56)	0.74	0.11
Hemoglobin concentration (µM)	-2.61 (-7.50, 2.28)	0.29	-1.20 (-6.00, 3.60)	0.62	0.57
Hemoglobin oxygenation (%)	1.70 (-3.49, 0.10)	0.06	-0.58 (-2.39, 1.23)	0.53	0.21
Left dorsolateral prefrontal cortex (n=119)					
Cerebral blood flow index (mm^2/s x10^{-8})	-0.12 (-1.04, 0.80)	0.80	-1.02 (-1.93, -0.11)	0.03	0.06
Cerebral oxygen metabolism index (au)	-0.52 (-4.02, 2.98)	0.77	-3.81 (-7.26, -0.37)	0.03	0.07
Hemoglobin concentration (µM)	0.80 (-3.13, 4.74)	0.69	1.95 (-1.88, 5.78)	0.31	0.57
Hemoglobin oxygenation (%)	-1.33 (-3.14, 0.48)	0.15	-0.23 (-1.99, 1.53)	0.80	0.23
Right dorsolateral prefrontal cortex (n=125)					
Cerebral blood flow index (mm^2/s x10^{-8})	0.45 (-0.45, 1.36)	0.32	0.35 (-0.55, 1.26)	0.44	0.83
Cerebral oxygen metabolism index (au)	2.22 (-1.61, 6.04)	0.25	1.14 (-2.66, 4.94)	0.55	0.58
Hemoglobin concentration (µM)	-3.28 (-7.01, 0.45)	0.08	-1.87 (-5.57, 1.82)	0.32	0.47
Hemoglobin oxygenation (%)	-1.74 (-3.41, -0.10)	0.04	-0.20 (-1.87, 1.47)	0.81	0.08
Per-protocol cohort					
Left ventrolateral prefrontal cortex (n=115)					
Cerebral blood flow index (mm^2/s x10^{-8})	1.21 (0.10, 2.34)	0.03	0.12 (-0.98, 1.22)	0.83	0.05
Cerebral oxygen metabolism index (au)	4.96 (0.98, 8.95)	0.02	0.57 (-3.34, 4.48)	0.77	0.03
Hemoglobin concentration (µM)	-1.86 (-6.52, 2.79)	0.43	-2.82 (-7.53, 1.88)	0.24	0.68
Hemoglobin oxygenation (%)	-2.06 (-3.76, -0.37)	0.02	-0.38 (-2.07, 1.31)	0.66	0.05
Right ventrolateral prefrontal cortex (n=112)					
Cerebral blood flow index (mm^2/s x10^{-8})	0.87 (0.04, 1.70)	0.04	0.15 (-0.69, 1.00)	0.72	0.09
Cerebral oxygen metabolism index (au)	3.14 (0.21, 6.06)	0.04	0.52 (-2.45, 3.48)	0.73	0.08
Hemoglobin concentration (µM)	-3.65 (-8.60, 1.32)	0.15	-1.94 (-6.90, 3.02)	0.44	0.49
Hemoglobin oxygenation (%)	-1.85 (-3.68, -0.02)	0.05	-0.82 (-2.70, 1.06)	0.39	0.26
Left dorsolateral prefrontal cortex (n=112)					
Cerebral blood flow index (mm^2/s x10^{-8})	0.10 (-0.82, 1.01)	0.83	-0.97 (-1.87, -0.10)	0.04	0.03
Cerebral oxygen metabolism index (au)	0.52 (-2.89, 3.93)	0.76	-3.41 (-6.79, -0.02)	0.05	0.03
Hemoglobin concentration (µM)	0.13 (-3.92, 4.19)	0.95	1.68 (-2.31, 5.67)	0.41	0.45
Hemoglobin oxygenation (%)	-1.58 (-3.47, 0.30)	0.10	-0.47 (-2.32, 1.38)	0.61	0.25
Right dorsolateral prefrontal cortex (n=118)					
Cerebral blood flow index (mm^2/s x10^{-8})	0.43 (-0.52, 1.38)	0.37	0.37 (-0.60, 1.33)	0.45	0.90
Cerebral oxygen metabolism index (au)	2.17 (-1.83, 6.17)	0.28	1.39 (-2.62, 5.39)	0.49	0.70
Hemoglobin concentration (µM)	-4.20 (-7.98, -0.42)	0.03	-3.86 (-7.69, -0.02)	0.05	0.86
Hemoglobin oxygenation (%)	-1.82 (-3.49, -0.14)	0.03	-0.81 (-2.51, 0.89)	0.34	0.26

CI, confidence interval; FBF, fortified blended food; NEWSUP, New Supplement.

[1]Calculated by linear mixed models that account for clustering of children within families. Each model is adjusted for age, sex, supplementation, baseline head circumference, and baseline measurement. [2]For comparison between NEWSUP and the Control group. [3]For comparison between FBF and the Control group. [4]For comparison between NEWSUP and FBF.

Supplementary Table G. Multivariable linear mixed models predicting 6-month changes from baseline in anthropometry and hemoglobin measures among children in the intention-to-treat cohort: an exploratory analysis of effect modification between supplementation and age group.

	NEWSUP Adjusted mean difference (95% CI)[1]	FBF Adjusted mean difference (95% CI)	Control Adjusted mean difference (95% CI)	*P* NEWSUP vs. Control	*P* FBF vs. Control	*P* NEWSUP vs. FBF	*P*$_{inter}$ group * agegroup
Hemoglobin (g/dL) among anemic children							
Children ≤ 3.9	0.96 (0.62, 1.29)	0.54 (0.22, 0.87)	0.31 (-0.03, 0.65)	0.003	0.25	0.04	0.40
Children > 4 years	0.83 (0.52, 1.14)	0.56 (0.26, 0.86)	0.54 (0.25, 0.83)	0.12	0.90	0.16	
Weight-for-age Z-score							
Children ≤ 3.9	-0.09 (-0.18, -0.01)	0.06 (-0.03, 0.16)	0.05 (-0.04, 0.14)	0.009	0.75	0.003	0.008
Children > 4 years	0.06 (-0.01, 0.13)	0.04 (-0.03, 0.11)	0.01 (-0.06, 0.08)	0.32	0.57	0.68	
Height-for-age Z-score							
Children ≤ 3.9	-0.35 (-0.44, -0.26)	-0.39 (-0.48, -0.29)	-0.30 (-0.40, -0.20)	0.36	0.14	0.52	0.21
Children > 4 years	-0.22 (-0.29, -0.14)	-0.24 (-0.32, -0.17)	-0.27 (-0.34, -0.20)	0.22	0.52	0.56	
BMI-for-age Z-score							
Children ≤ 3.9	0.25 (0.12, 0.38)	0.50 (0.36, 0.64)	0.44 (0.30, 0.58)	0.02	0.46	0.003	0.03
Children > 4 years	0.29 (0.18, 0.40)	0.29 (0.18, 0.40)	0.27 (0.16, 0.38)	0.77	0.77	>0.99	
Mid-upper arm circumference (cm)							
Children ≤ 3.9	0.05 (-0.09, 0.19)	0.20 (0.05, 0.35)	0.24 (0.09, 0.38)	0.03	0.66	0.08	0.35
Children > 4 years	0.09 (-0.03, 0.21)	0.17 (-0.06, 0.29)	0.12 (0.01, 0.24)	0.64	0.50	0.26	
Lean tissue area (cm^2)							
Children ≤ 3.9	2.01 (-1.26, 5.27)	-1.02 (-4.52, 2.49)	0.70 (-2.77, 4.16)	0.52	0.42	0.14	0.14
Children > 4 years	7.34 (4.57, 10.12)	2.96 (0.21, 5.71)	1.14 (-1.54, 3.82)	0.0004	0.30	0.01	
Fat tissue area (cm^2)							
Children ≤ 3.9	0.36 (-4.82, 5.54)	6.88 (1.32, 12.44)	6.19 (0.69, 11.69)	0.07	0.84	0.04	0.94
Children > 4 years	-5.16 (-9.51, -0.81)	0.53 (-3.79, 4.84)	1.32 (-2.89, 5.54)	0.02	0.77	0.04	

BMI, body mass index; CI, confidence interval; FBF, fortified blended food; MUAC, mid-upper arm circumference; NEWSUP, New Supplement.

[1]Adjusted mean differences from baseline within each group calculated by linear mixed models accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline measurement, and the interaction between treatment group and age group.

Supplementary Table H. Multivariable linear mixed models predicting 6-month changes in anthropometry and hemoglobin measures among children in the per-protocol cohort: an exploratory analysis of effect modification between supplementation and age group.

	NEWSUP Adjusted mean difference (95% CI)	FBF Adjusted mean difference (95% CI)	Control Adjusted mean difference (95% CI)	*P* NEWSUP vs. Control	*P* FBF vs. Control	*P* NEWSUP vs. FBF	*P*$_{inter}$ group * agegroup
Hemoglobin (g/dL) among anemic children							
Children ≤ 3.9	1.07 (0.70, 1.44)	0.49 (0.13, 0.85)	0.30 (-0.08, 0.69)	0.002	0.40	0.01	0.32
Children > 4 years	0.77 (0.45, 1.10)	0.48 (0.17, 0.79)	0.44 (0.13, 0.74)	0.09	0.83	0.13	
Weight-for-age Z-score							
Children ≤ 3.9	-0.09 (-0.18, 0.01)	0.05 (-0.05, 0.15)	0.07 (-0.03, 0.17)	0.009	0.76	0.02	0.01
Children > 4 years	0.06 (-0.01, 0.14)	0.04 (-0.03, 0.12)	0.02 (-0.05, 0.09)	0.36	0.61	0.68	
Height-for-age Z-score							
Children ≤ 3.9	-0.36 (-0.46, -0.26)	-0.37 (-0.47, -0.26)	-0.30 (-0.41, -0.19)	0.32	0.30	0.93	0.22
Children > 4 years	-0.19 (-0.26, -0.11)	-0.22 (-0.29, -0.14)	-0.26 (-0.33, -0.18)	0.16	0.45	0.52	
BMI-for-age Z-score							
Children ≤ 3.9	0.26 (0.12, 0.40)	0.48 (0.33, 0.63)	0.46 (0.31, 0.61)	0.02	0.84	0.01	0.07
Children > 4 years	0.27 (0.16, 0.38)	0.27 (0.15, 0.38)	0.26 (0.15, 0.37)	0.94	0.94	>0.99	
Mid-upper arm circumference (cm)							
Children ≤ 3.9	0.05 (-0.10, 0.20)	0.22 (0.06, 0.38)	0.28 (0.12, 0.44)	0.01	0.51	0.08	0.35
Children > 4 years	0.10 (-0.02, 0.22)	0.19 (0.07, 0.31)	0.16 (0.05, 0.28)	0.43	0.70	0.24	
Lean tissue area (cm^2)							
Children ≤ 3.9	2.17 (-1.49, 5.84)	-1.77 (-5.66, 2.13)	1.04 (-2.84, 4.92)	0.62	0.23	0.09	0.14
Children > 4 years	7.03 (4.08, 9.98)	2.54 (-0.39, 5.46)	0.87 (-1.99, 3.73)	0.001	0.37	0.02	
Fat tissue area (cm^2)							
Children ≤ 3.9	0.26 (-5.54, 6.06)	7.95 (1.80, 14.11)	6.97 (0.83, 13.11)	0.06	0.79	0.03	0.88
Children > 4 years	-4.58 (-9.15, -0.001)	1.46 (-3.08, 6.00)	2.70 (-1.75, 7.15)	0.01	0.67	0.04	

BMI, body mass index; CI, confidence interval; FBF, fortified blended food; MUAC, mid-upper arm circumference; NEWSUP, New Supplement.

[1]Adjusted mean differences from baseline within each group calculated by linear mixed models accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline measurement, and the interaction between treatment group and age group.

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